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Health in Action

Pregnancy Exposure Registries for Assessing Antimalarial Drug Safety in Pregnancy in Malaria-Endemic Countries

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Summary Points

- There is an urgent need to develop targeted pharmacovigilance systems to assess the safety of antimalarials in early pregnancy.
- The artemisinins are effective antimalarials increasingly deployed in malaria-endemic countries; however, they have been shown to be embryo-toxic in animal models, and their safety in early human pregnancies remains uncertain.
- Modelling suggests that the probability an embryo will encounter artemisinins during the critical six-week period (at week four to week ten of gestation) through accidental exposure is 12% for areas where adults receive on average one treatment with three days of artemisinin-based combination therapy per year.
- Most of the approaches used in industrialised countries to evaluate a drug's embryo-foetal toxicity have limited application in resource-poor countries. Establishing an international antimalarial pregnancy exposure registry would enable a targeted prospective pharmacovigilance approach and timely assessment of the risk–benefit profile of antimalarials.
- Here we discuss methodological considerations for the systematic prospective assessment of pregnancy outcomes and congenital malformations in women exposed to antimalarials early in pregnancy, including approaches to capture drug exposure information in resource-poor settings, choice of comparison groups, and sample size considerations.

Because pregnant women are routinely excluded from pre-licensure clinical trials for fear of harming the mother or the developing foetus [1], most drugs are marketed with limited information on their safety during pregnancy and therefore are not recommended for use by pregnant women. Yet drugs are widely used by pregnant women, and medication often cannot be avoided in chronic diseases such as epilepsy and HIV or other acute illness that harm the mother and the unborn child if left untreated.

Passive mechanisms of spontaneous reporting of adverse drug effects are inadequate for detecting drug-induced foetal risks or lack of such risks [2]. The US Food and Drug Administration and the European Medicine Agency recommend active surveillance, such as the use of pregnancy exposure registries (PERs), for products that are likely to be used during pregnancy or by women of childbearing age (WOCBAs), particularly if there have been case reports of adverse pregnancy outcome following exposure, if drugs in the same pharmacological class are known to pose risk during pregnancy, or if pre-clinical animal data suggest potential teratogenic risk [3,4]. In industrialised countries, this information can be derived from medical records and automated databases, including medical or pharmacy insurance claims. Such approaches are challenging in developing countries where resources for routine pharmacovigilance are rare and automated data sources generally do not exist [5–8]. Thus, nearly all developing countries rely on drug safety data from industrialised countries. However, there are often no or limited safety data in pregnancy for drugs targeting tropical diseases, as these are not widely used in the countries with more robust pharmacovigilance systems [9].

Antimalarials are a good example [9]. Malaria can have devastating consequences for the mother and foetus [10,11], and pregnant women require prompt treatment with safe and effective antimalarial drugs when infected. The artemisinins are among the most effective and rapidly acting antimalarials to date, providing life-saving benefits to children, adults, and

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Abbreviations: ACT, artemisinin combination therapy; PER, pregnancy exposure registry; WHO, World Health Organization; WOCBA, woman of childbearing age

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Box 1. Mechanism of Artemisinin Toxicity in Early Pregnancy

Animal reproductive toxicology studies show that artemisinin derivatives all have embryo-toxic effects at low-dose ranges in all species studied (i.e., mice, rat, rabbit, frog, and primate models) [31–34].The embryo-toxic mechanism is thought to occur through depletion of embryonic erythroblasts (primitive erythrocytes), which is associated with severe anaemia leading to cell damage and death due to hypoxia [35]. In humans, the most sensitive time window may be between week four and week ten, when erythroblasts circulate and have not yet been fully replaced by definitive erythrocytes [36]. In addition to the window of sensitivity, the duration of exposure is also important. Rodents have a synchronous clonal expansion of metabolically active erythroblasts, making them particularly vulnerable during a three- to four-day window early in pregnancy. In primates (and most likely also in humans), this may not be the case, as different generations of erythroblasts co-exist and are progressively replaced by definitive erythrocytes over a period of weeks [35]. In cynomolgus monkeys, no embryo lethality or malformations were observed with three-day exposures (the typical duration of treatment with ACTs) or with seven-day exposures [31,32,35,36]. The predictive value of the animal models for humans is unclear, particularly because the duration of daily exposure is likely to be short (hours) as the artemisinins are rapidly eliminated and limited to three or at maximum seven days.

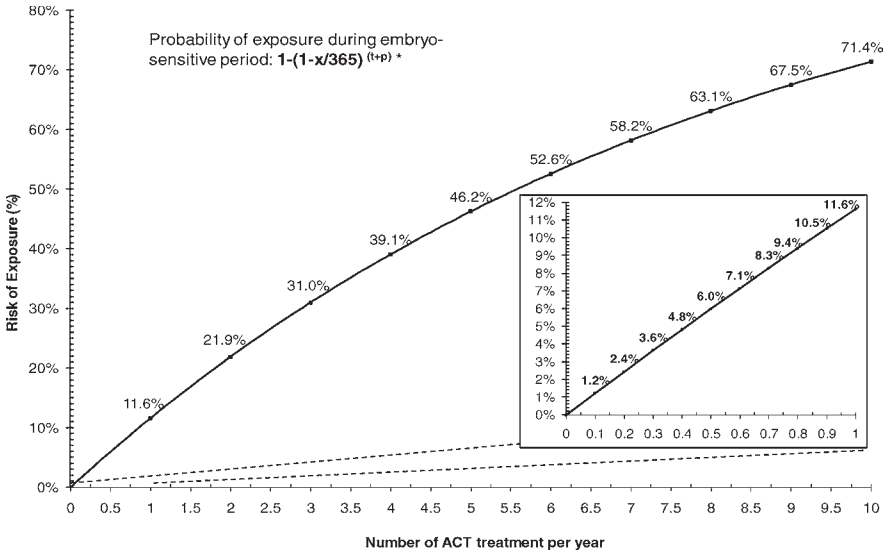

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Figure 1. Probability that an Embryo Will Encounter Artemisinins Inadvertently During the Critical Six-Week Period of Its Development (Week Four to Week Ten), According to the Average Number of ACT Treatments Received Per Year

In the figure, x = number of treatments per year, t = embryo-sensitive period in days (set as 42 days or six weeks), and p = period of treatment and persistence of drug (set as three days because ACTs are normally deployed as a three-day regimen and artemisinins are eliminated within hours after each dose). The inadvertently exposed group will consist of women taking ACTs for confirmed malaria and for presumed malaria. It has been estimated that over 70% of malaria episodes in rural Africa and about 50% in urban areas are self-treated without consulting trained professionals [39]. Thus, many of these will be presumptive treatments without involvement of the formal health services, diagnostic confirmation of malaria, or screening for potential pregnancy. Even if more women seek treatment at health facilities with the deployment of more expensive ACTs and rapid diagnostic tests, antimalarials are often administered disregarding any diagnostic test. Studies in Africa indicated that between 30% and 50% of patients with a negative diagnostic test (microscopy or rapid diagnostic test) were still prescribed antimalarial drugs [40,41]. These proportions are likely to increase further when successful malaria control reduces malaria exposure. (Adapted from [16].)

pregnant women [12]. The limited information regarding their safety is reassuring [13], and the World Health Organization (WHO) now recommends the use of artemisinin combination therapies (ACTs) in the second and third but not yet in the first trimester (unless alternatives are not available) [12], as uncertainty remains about their safety in early pregnancy (Box 1) [14–16]. ACTs are rapidly being rolled out and may soon become among the most widely used antimalarial drugs. Because there are no specific risk management precautions to exclude WOCBAs from using ACTs, the potential for inadvertent exposure to artemisinins early in pregnancy is high and in many cases unavoidable (Figure 1). Health care providers, pregnant women, and policy makers urgently need valid information to make informed decisions about the risks and benefits of ACTs for WOCBAs.

This paper describes the use of PERs as a targeted pharmacovigilance approach for assessing the safety of antimalarial drugs used during early pregnancy in resource-constrained malaria-endemic countries.

Antimalarial Pregnancy Exposure Registries

PERs are the most common approach used to monitor drug safety in pregnancy and provide reassurance on the potential risk associated with certain drugs. They can serve both to generate hypotheses and to evaluate suspected risks or risk factors that may have been identified during pre- or post-marketing phases [2]. In industrialised countries, 32 PERs are registered with the Food and Drug Administration [17]. There is some variation in design, but they all use prospective approaches and identify and follow exposed women until the end of pregnancy (i.e., before the outcome is known). The systematic prospective ascertainment of pregnancy outcomes has several major advantages over case-control designs and passive surveillance. This design reduces selection bias (for example, due to self-reporting) and recall bias, has the potential to use standardised methods to assess outcome, and—because of the availability of both numerator and denominators—allows calculations of risk estimates that can then be compared against comparison groups or background population rates [2]. One other attractive feature of PERs is that they can be time-limited and terminated once the target sample size to rule out a pre-defined risk is reached.

Assessment of Drug Exposure and Record Linkage

The design for reliably capturing the occurrence and timing of inadvertent drug exposure to ACTs in early pregnancy requires special consideration. Firstly, the critical period occurs around the time when many women may not yet be aware of their pregnancy (our current understanding from animal models of the mechanism of embryotoxicity of the artemisinins suggests that in humans the sensitive drug exposure time window is between week four to week ten of gestation [Box 1]). Secondly, retrospective determination of the precise timing of exposure is challenging since a typical treatment course is short (three days). Another difficulty is the accurate assessment of the gestational age at the time of exposure. Lastly, malaria treatment is often home-based or unsupervised and antimalarials can be obtained from a variety of providers, often over-the-counter. In contrast, antiretroviral and anti-tuberculosis drugs are typically provided by formal health services, which are more likely to keep records. Furthermore, exposures are often long-term and continuous, making it easier to determine if and when a woman was exposed to antiretroviral or anti-tuberculosis medication than with the short course of antimalarials.

Although most exposures to artemisinins in early pregnancy will be unintentional, deliberate exposures can occur where the benefit is perceived to outweigh the potential risk, as recommended by WHO (such as for severe life-threatening malaria) [12]. Either way, reliable ascertainment of drug exposure will require record linkage. This can be done using prospective approaches by linking datasets containing drug dispensing information (e.g., malaria treatment records from out-patient departments) to datasets that capture newly identified pregnancies (e.g., from antenatal clinics or demographic surveillance systems). This can determine whether a WOCBA might have been pregnant at the time of treatment. Alternatively, records of pregnant women can be linked retrospectively with their earlier treatment records. A disadvantage of recruiting pregnant women rather than WOCBAs is that miscarriages will be missed, as the pregnancy may not be sustained long enough for women to attend antenatal care. The pregnant woman's drug history should be taken to verify the record linkage and to capture information on any drug use not dispensed through formal pharmacies.

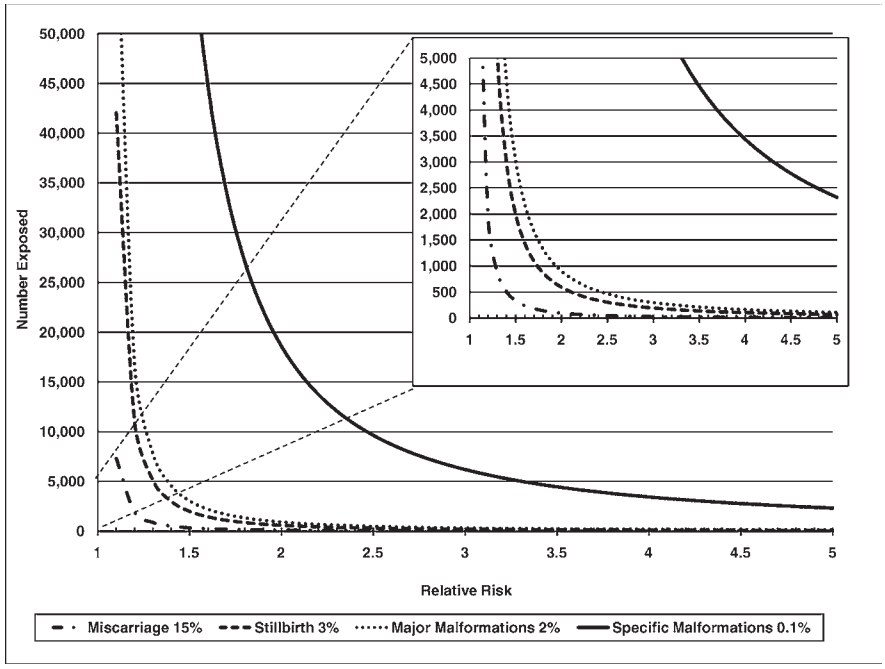

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Figure 2. Sample Size Calculation for Pregnancy Exposure Registry by Defect Frequency and Detectable Difference

Exposed to comparison group ratio = 1:1, power = 80%, and one-sided $\alpha = 0.05$. Based on the formula for cohort design described in Strom's *Pharmacoepidemiology* [25]: $N = 1/[p(1 - R)]^2 \times [Z_{1-\alpha}\sqrt{((1 + 1/k)U(1 - U)) + Z_{1-\beta}\sqrt{(pR(1 - Rp) + (P(1 - P))/k)}}]^2$ where p is the incidence of disease in unexposed; R is the minimum relative risk to detect; k is the ratio of unexposed controls to exposed, and $U = (Kp + pR)/(k + 1)$.

Pregnancy Outcome Assessment

The primary outcome of interest is a decisive factor for the choice of study design, study population, and target data sources for outcome ascertainment and needs to be defined a priori. Although pre-approval animal reproductive toxicology studies have ambiguous predictive value for human embryo-foetal toxicity, due to variations in species-specific effects [18], the current data from animal models suggest that the effects are not species-specific and that exposure early in the first trimester might cause birth defects and/or early embryo/foetal death with subsequent miscarriages or foetal resorption. Most of the existing PERs monitor all pregnancy outcomes (i.e., live births, still births, and miscarriages), but the design and sample size calculation focus on capturing birth defects [19]. Foetal resorption and early miscarriages are very difficult to assess reliably; most will go unnoticed clinically as they occur before eight to nine weeks, with the majority occurring before three weeks [20]. Only repeated pregnancy testing with a switch from positive to negative tests may suggest objectively early loss of pregnancy [21]. This is unlikely to be feasible or culturally acceptable in many malaria-endemic countries, and the frequent use of pregnancy testing itself reduces the probability of inadvertent exposures in that population. We may thus have to accept that early pregnancy loss cannot be captured reliably in sufficient numbers, in contrast to later miscarriages and stillbirths.

For birth defects, the duration of follow-up of the infant needs to be considered carefully, since only about half of major structural and functional defects in children can be detected or classified at birth [22,23]. The prevalence also varies with the specific defect inclusion and exclusion criteria and whether the case definition includes developmental, functional, or other types of congenital disorders (e.g., non-structural

Box 2: Probability that a Woman of Childbearing Age Treated for Malaria at an Out-Patient Clinic Had an Undetected Pregnancy of Four to Ten Weeks Gestation

An approximation of the probability that a WOCBA attending an out-patient clinic has an early pregnancy can be indirectly estimated from published total fertility rates. For sub-Saharan Africa, total fertility rate was 5.5 in 2004 [37] and is defined as the number of live-born children an average women would have, assuming that she lives her full reproductive lifetime of 35 years (1,820 weeks, from 15 to 49 years). The total pregnancy rate (6.7) was then calculated as the total fertility rate (5.5) multiplied by a factor of 1.22 (1 / [1.0 – 0.15 – 0.03]) to take into account 15% pregnancy loss due to miscarriages (a conservative estimate) and 3% due to stillbirths (the average rate of stillbirths observed in developing countries [38]). Thus, of 1,820 reproductive weeks, a woman is pregnant for 268 weeks (6.7 × 40 weeks); of which 40.2 weeks (6.7 × 6 weeks) are during the sensitive six-week time window from week four to week ten of gestation. Under these conditions, 14.7% (268 of 1,820) of WOCBAs are pregnant at any time (i.e., one in 6.8), and 2.2% (40.2 of 1,820) or one in 45 are pregnant between week four and week ten.

If accidental exposure is defined as unintentional treatment in early pregnancy only, than the risk of accidental exposure is slightly higher than 2.2%, as later pregnancy weeks do not contribute to the denominator. The average time for women in Africa to recognise and report a pregnancy is not well described in settings where pregnancy testing is not readily available. If it is assumed that this is during the first ten weeks of pregnancy, then the denominator is 1,619 weeks (the 1,552 weeks that she is not pregnant [1,820 – 268] plus the 67 weeks of early pregnancy (6.7 pregnancies × 10 weeks), and the risk of accidental exposure in the four- to ten-week period is 40.2 out of 1,607 weeks or 2.5% (one in 40 women).

This assumes that the probability of getting clinical malaria is the same in these first ten weeks of pregnancy as in non-pregnant women.

genetic disorders) [24]. Assessment of congenital malformation requires careful examination by dedicated staff trained to examine newborns using a standard tool and scoring system. Suspected birth defects could be reviewed by a centralised committee that included dysmorphologists and other specialists (e.g., using digital photographs). Complimentary visiting specialists could study additional outcomes such as cardiovascular and neuro-developmental defects and other potential long-term effects in a selected sample later in infancy.

Comparison Groups

Assessing the teratogenic potential of a drug requires comparison of the frequency of birth defects against other groups to put a signal into context. These comparison groups can be external (i.e., from peripheral sources) or internal (i.e., generated from within the same study or system).

External population data from national health statistics centres and/or birth defects surveillance systems are commonly used as sources to calculate background event rates. This type of external comparison data is not currently available in most malaria-endemic countries. Furthermore, these comparisons need to be interpreted with caution as many confounding factors or potential effect modifiers of risk may differ from the exposed group of interest [2,25].

Internal comparison groups can consist of women with the same conditions who are unexposed to drugs (in which case the possibility of confounding by indication should be taken into account), exposed to a different drug with established safety, or exposed to the same investigational drug, but only outside the critical period (e.g., in the second or third trimesters).

Sample Size Calculation

The main determinants of sample size are the degree of the teratogenic effect to be excluded (relative risk) and the expected frequency of the endpoint of interest in the non-exposed group (Figure 2). A third factor is the type and number of potential controls. For example, with an exposed/unexposed ratio of 1:4, approximately 522 exposed women and 2,090 unexposed women are needed to exclude a 2-fold increase in major malformations detectable at birth when the predicted rate in the comparison group is 2% (power 80%, alpha 0.05). This would be 10,748/42,992 exposed/unexposed women for birth defects that occur at a frequency of one in 1,000 (such as cleft lip/palate). Such numbers will only be achievable using several sentinel sites over several years. The sample sizes will also need to account for loss to follow-up and the fact that not all births can be examined for birth defects (e.g., foetal loss with discarding of expelled foetus prior to examination by study staff). The rate of recruitment will depend on the likelihood of accidental exposure. This depends on the fertility rate and frequency of drug exposure in the population. For example, in areas where pregnancy testing is not available, the average number of ACT treatments is one per woman per year, and the total fertility rate is 5.5, the probability is only 2.5% (or one in 40 women) (Box 2; see Text S1).

Concomitant Medication

Although the registry could be set up initially to address the specific question of the safety of antimalarials in pregnancy, it is essential to capture concomitant diseases and medications such as antiretrovirals because of potential drug interactions, confounding, and effect modification. As such, these additional data could contribute to PERs for other diseases such as the Antiretroviral Pregnancy Registry [26,27].

Data Sources

There are many methodological challenges to designing PERs for antimalarials, including those common to most pharmacovigilance methods in resource-poor countries [28,29]. The specialised nature of the reliable assessment of drug exposure and congenital malformations is not easily achievable from routine pharmacovigilance surveillance systems (where they exist). Such an effort will require dedicated sentinel sites that are capable of following WOCBAs and linking antenatal care records with treatment records, such as sites with demographic health surveillance systems or sites with captive populations where health care is provided centrally and well recorded (e.g., industrial and agricultural estates or long-term refugee camps).

While the primary source of information is prospective and observational, data from clinical trials and other studies involving pregnant women, and retrospective case series (i.e., pregnancies with a known outcome at the time of reporting) could be included as secondary data and analysed separately, as is currently done with some of the existing PERs [30].

Conclusion

The establishment of an international antimalarial pregnancy exposure registry, using specialised sentinel sites to provide reliable exposure and outcome data for the primary data collection, is a potentially cost-effective targeted approach. Central collation of the information would enable evaluation of the risk–benefit profile of antimalarials in a timely manner, and over time would allow the detection of rare adverse drug reactions that could not be detected by any single study. New levels of collaboration between pharmacovigilance programmes, antimalarial drug developers, research groups, regulatory authorities, and WHO will be essential. This international multi-product, multi-sponsor approach will require good governance structures, such as those used by the Antiretroviral Pregnancy Registry, and if successful could serve as a pathfinder for other PERs to capture much-needed safety information on other drugs used for tropical diseases [9]. ■

Supporting Information

Text S1. A longer, more detailed version of this paper

Found at doi:10.1371/journal.pmed.0050187.sd001 (596 KB DOC).

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